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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,950	08/17/2000	Josef Burg	HUBR-1159	9456

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EXAMINER
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AUDET, MAURY A

ART UNIT	PAPER NUMBER
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1654

DATE MAILED: 09/09/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/555,950

Applicant(s)

BURG ET AL.

Examiner

Maury Audet

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-- Th MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 30 June 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 43-87 is/are pending in the application.
- 4a) Of the above claim(s) 64-87 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 43-63 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

**DETAILED ACTION*****Election/Restrictions***

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that Fibi et al. does not establish a lack of unity. This is not found persuasive because Fibi et al., as discussed, does teach the special technical feature, erythropoietin in composition.

The following references are cited as further support. The alleged special technical feature of Groups I-III is EPO in composition. Watson et al. teach that recombinant EPO from CHO cells contains 82% tetraantennary oligosaccharides which are 95% sialylated. The tetraantennary oligosaccharides contain between 4 and 7 (i.e. an average of 5.5) N-acetyl lactosamine units, based on an N-bound carbohydrate chain (page 227, column 2, 2<sup>nd</sup> ¶ middle; Table II; entire document). Also, Takeuchi et al. teach a standard EPO composition from CHO which contains 80% tetraantennary oligosaccharides (1<sup>st</sup> ¶; entire document). Additionally, Nimtz et al. teach that recombinant EPO from BHK cells contains over 82% tetraantennary structures. Nimtz also teaches that tetraantennary structures contain at least 4 N-acetyl lactosamine units, based on an N-bound carbohydrate chain (abstract; entire document). [See also PCT/EP 98/07876 International Preliminary Examination Report, and references therein, included as part of present application]. Therefore, the special technical feature (EPO in composition) that links the inventions (and core to independent claims 43-44, and 46-47) does not "define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art". Thus, Groups I-III are subject to a lack of unity requirement and restriction is proper.

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The requirement is still deemed proper and is therefore made FINAL.

Claim 43-63 (Group I) are examined on the merits. Claims 64-87, drawn to non-elected subject matter, are withdrawn from further consideration.

### ***Claim Objections***

Claims 61 and 62 are objected to because of the following informalities: the claims depend from claims 55 and 58 respectively, but the word "claim" before each has been omitted.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Based in particular on claims 43-44 and 46-47, it is unclear what the invention really is, since the separate, independent claims all appear to be claiming the same subject matter through mutually divergent definitions (as also observed by the European Examining Authority in PCT/EP 98/07876 International Preliminary Examination Report). As stated in the references above, obtaining a CHO composition by culturing it from CHO, which has high specific activity based on increased glycosylation (i.e. N-acetyl-lactosamine units) is known. *It is unclear what Applicant is claiming, since the same composition from the same source is described, and the*

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*claims do not indicate how or where on the EPO compound more N-acetyl lactosamine units have been added, to purportedly increase the glycosylation of the EPO compound over EPO compound/compositions known in the art?*

Additionally, it is unclear how the subject matter of any one of these claims 43-44 and 46-47 further defines the invention over what is asserted to be defined in any of the other claims.

Furthermore, it is not understood, in claims 45 and 48, if the term carbohydrate after (i) is to refer to only "N-acetyl lactosamine", and if "EPO" after (ii) is to refer to , confound the confusion, by referring to (i) as carbohydrate, and (ii) is to refer to "N-acetyl lactosamine units" as well.

Based on the above, and the claim language used in attempting to define the single invention in four separate ways (claims 43-44, and 46-47), the metes and bounds of the invention are unclear. Most importantly, this renders a third party's practices unclear as to whether the lack of infringement of one of claims 43-44 and 46-47, would not in fact infringe one of the other claims.

It is suggested that Applicant consolidate the four independent claims into a single claim and distinctly claim the subject matter of the invention; namely where on the EPO compound the structure has been altered (as opposed to merely including all four different definitions in one claim, without clarification).

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 43-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Watson et al. (Glycobiology, 1994, 4(2): 227-37).

Watson et al. teach that EPO is produced in CHO cells (page 227, column 2, 2<sup>nd</sup> ¶ middle; Table II; entire document).. Thus, the claimed EPO and composition is inherently produced

Claims 43-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Takeuchi et al. (Proc. Natl. Acad. Sci., October 1989, 86: 7810-7822).

Takeuchi et al. teach a standard EPO composition from CHO cells which contains 80% tetraantennary oligosaccharides in a substance (1<sup>st</sup> ¶; entire document). Takeuchi also teach that higher branching of the N-linked sugar chains is essential for effective expression [specific

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activity] of in vivo biological activity of EPO (abstract). Thus, the claimed EPO and composition is inherently produced.

Claims 43-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Blumen et al. (US 5,459,031).

Blumen et al. teach increased glycosylated recombinant EPO in composition produced in CHO cell culture (col. 10, lines 22-24; claims).

Claims 43-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Akamatsu et al. (US 4,745,099).

Akamatsu et al. teach EPO in composition and cultured from CHO (col. 2, lines 49-50, and 64-67). Thus, the claimed EPO and composition is inherently produced.

Claims 43-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Nimtz et al. (Eur. J. Biochem., 1993, 213: 39-56).

Nimtz et al. teach that recombinant EPO, even from BHK cells, contains over 82% tetraantennary structures. Nimtz et al. also teach that tetraantennary structures contain at least 4 N-acetyl lactosamine units, based on an N-bound carbohydrate chain in a substance (abstract; entire document). Thus, the claimed EPO and composition is inherently produced.

Claims 43-63 are rejected under 35 U.S.C. 102(e) as being anticipated by Strickland et al. (5,856,298).

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Strickland et al. teach EPO in composition, in various isoforms having a specific number of sialic acids, and thus specific glycosylation levels, per EPO molecule (abstract, entire document). Strickland also teach EPO cultured from CHO (col. 19, lines 18-42). Thus, the claimed EPO and composition is inherently produced.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 43-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watson et al. (Glycobiology, 1994, 4(2): 227-37), Takeuchi et al. (Proc. Natl. Acad. Sci., October 1989, 86: 7810-7822), Blumen et al. (US 5,459,031), Akamatsu et al. (US 4,745,099), Nimtz et al. (Eur. J. Biochem., 1993, 213: 39-56), or Strickland et al. (5,856,298) in view of EP-A-0 267 678 (Integrated Genetics, Inc.) and Hokke et al. (Eur. J. Biochem. 1995, 228: 981-1008).

Watson et al., Takeuchi et al., Blumen et al., Akamatsu et al., Nimtz et al., and Strickland et al. are all discussed above.

EP-A-0 267 678 teach the continuous production of EPO in a serum-free medium (bottom page 5, entire document).

Hokke et al. teach that a high degree of sialylation (tetraantennary carbohydrate chains) leads to a high level of activity (page 1004, right column, lines 6-14).



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It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a serum free medium of EP-A-0 267 678 to glycosylate/sialylate to various degrees the EPO compositions of Watson et al., Nimtz et al., and Takeuchi et al., because EP-A-0 267 678 has shown the advantageous use of a serum free medium to glycosylate EPO composition.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made that increased specific activity as shown in Hokke et al. would have resulted from the increased glycosylated/sialylated EPO compositions of Watson et al., Nimtz et al., and Takeuchi et al., because both Hokke et al. and Takeuchi et al. (discussed above; and intrinsically Watson et al. and Nimtz et al.) taught the advantageous increase in in vivo specific activity with increased sialylation of the EPO composition.

Additionally, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to arrive at various degrees of glycosylation (and/or amounts of N-acetyl lactosamine units), and hence increased specific activity, in the EPO compositions of Watson et al., Nimtz et al., and Takeuchi et al., because the references teach the advantageous use of methods to vary the degrees of glycosylation in the EPO compositions. Where tetraantennary structures *undergo virtually complete sialylation* (as described in the prior art references), *the product of the number of N-acetyl lactosamine units, based on a N-bound carbohydrate chain, and the sialic acid content per molecule is at least 48 (4LU x 12SA).* Furthermore, this figure is even higher in the known EPO compositions as a result of additional N-acetyl lactosamine unit repeats.

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Thus, if not intrinsically taught in the above references, all of Applicant's glycosylation/sialylation percentage adjustments (as well as the culture medium being serum free) to the EPO composition would have been within the purview of one of skill in the art, in view of each of the references, since all the variations are merely routine optimizations of the base EPO composition, which each of the references independently teaches.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.


No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA; September 2, 2003

  
**MICHAEL MELLER**  
**PRIMARY EXAMINER**